Hydroxocobalamin and Epinephrine Both Improve Survival in a Swine Model of Cyanide-Induced Cardiac Arrest

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Study objective: To determine whether hydroxocobalamin will improve survival compared with epinephrine and saline solution controls in a model of cyanide-induced cardiac arrest.

Methods: Forty-five swine (38 to 42 kg) were tracheally intubated, anesthetized, and central venous and arterial continuous cardiovascular monitoring catheters were inserted. Potassium cyanide was infused until cardiac arrest developed, defined as mean arterial pressure less than 30 mm Hg. Animals were treated with standardized mechanical chest compressions and were randomly assigned to receive one of 3 intravenous bolus therapies: hydroxocobalamin, epinephrine, or saline solution (control). All animals were monitored for 60 minutes after cardiac arrest. Additional epinephrine infusions were used in all arms of the study after return of spontaneous circulation for systolic blood pressure less than 90 mm Hg. A sample size of 15 animals per group was determined according to a power of 80%, a survival difference of 0.5, and an α of 0.05. Repeated-measure ANOVA was used to determine statistically significant changes between groups over time.

Results: Baseline weight, time to arrest, and cyanide dose at cardiac arrest were similar in the 3 groups. Coronary perfusion pressures with chest compressions were greater than 15 mm Hg in both treatment groups indicating sufficient compression depth. Zero of 15 (95% confidence interval [CI] 0% to 25%) animals in the control group, 11 of 15 (73%; 95% CI 48% to 90%) in the hydroxocobalamin group, and 11 of 15 (73%; 95% CI 48% to 90%) in the epinephrine group survived to the conclusion of the study ($P<.001$). The proportion of animals with return of spontaneous circulation at 5 minutes was 4 of 15 (27%; 95% CI 10% to 52%), and that of return of spontaneous circulation at 10 minutes was 11 of 15 (73%; 95% CI 48% to 90%) in the 2 treatment groups. Additional epinephrine infusion after return of spontaneous circulation was administered for hypotension in 2 of 11 (18%; 95% CI 4% to 48%) hydroxocobalamin animals and in 11 of 11 (100%; 95% CI 70% to 100%) of the epinephrine animals ($P<.001$). At 60 minutes, serum lactate was significantly lower in the hydroxocobalamin group compared with the epinephrine group (4.9 [SD 2.2] versus 12.3 [SD 2.2] mmol/L), and the pH was significantly higher (7.34 [SD 0.03] versus 7.15 [SD 0.07]). Serial blood cyanide levels in the hydroxocobalamin group were also lower than that of the epinephrine group from cardiac arrest through the conclusion of the study.

Conclusion: Intravenous hydroxocobalamin and epinephrine both independently improved survival compared with saline solution control in our swine model of cyanide-induced cardiac arrest. Hydroxocobalamin improved mean arterial pressure and pH, decreased blood lactate and cyanide levels, and decreased the use of rescue epinephrine therapy compared with that in the epinephrine group. [Ann Emerg Med. 2012;60:415-422.]

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INTRODUCTION
Background

Cyanide is considered an uncommon cause of death, but in 2007 the American Association of Poison Centers reported 5 deaths from cyanide, similar to the number of deaths reported for digoxin, β-blockers, and pesticides and herbicides.[1] In addition to intentional poisoning, cyanide can also cause toxicity and death from exposure to smoke. More than 15,000 people per year are injured in house fires, and 6,000 of these die.[2] Recent evidence suggests that many of these immediate deaths are due to inhaled cyanide.[3,4] Finally, cyanide is a terrorist threat, and several federal agencies have recommended additional study of cyanide antidotes because of recent thwarted terrorist attempts at dispersing cyanide.[5-8]

Report Documentation Page		Form Approved OMB No. 0704-0188

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1. REPORT DATE **01 OCT 2012**	2. REPORT TYPE **N/A**	3. DATES COVERED **-**	
4. TITLE AND SUBTITLE **Hydroxocobalamin and epinephrine both improve survival in a swine model of cyanide-induced cardiac arrest**		5a. CONTRACT NUMBER	
		5b. GRANT NUMBER	
		5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) **Bebarta V. S., Pitotti R. L., Dixon P. S., Valtier S., Esquivel L., Bush A., Little C.,**		5d. PROJECT NUMBER	
		5e. TASK NUMBER	
		5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX**		8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)		10. SPONSOR/MONITOR'S ACRONYM(S)	
		11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT **Approved for public release, distribution unlimited**			
13. SUPPLEMENTARY NOTES			
14. ABSTRACT			
15. SUBJECT TERMS			

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT **UU**	18. NUMBER OF PAGES **8**	19a. NAME OF RESPONSIBLE PERSON
a. REPORT **unclassified**	b. ABSTRACT **unclassified**	c. THIS PAGE **unclassified**			

Editor's Capsule Summary

What is already known on this topic
The effectiveness of the cyanide antidote hydroxocobalamin has not been evaluated in cyanide-induced cardiopulmonary arrest.

What question this study addressed
Clinical indices and survival were measured in a clinically relevant randomized, blinded swine model of cyanide-induced cardiac arrest with 3 experimental groups: hydroxocobalamin, epinephrine, or saline solution (control).

What this study adds to our knowledge
Survival was 0 of 15 in the control group, 11 of 15 in the hydroxocobalamin group, and 11 of 15 in the epinephrine group. The hydroxocobalamin group had improved mean arterial pressure and pH, with decreased blood lactate and blood cyanide levels compared with the epinephrine group.

How this is relevant to clinical practice
Hydroxocobalamin and epinephrine both independently improved survival. Clinical indicators improved more quickly in the hydroxocobalamin group, but the clinical significance of this finding is unknown.

Cyanide's clinical effects are rapid and can produce tachycardia, profound hypotension, and cardiac arrest. Shock and cardiac arrest are common and develop in up to 50% of cyanide-exposed patients.[9,10] Most victims who develop cardiopulmonary arrest die if they do not receive an antidote.[9] However, cyanide-induced cardiac arrest has not been rigorously investigated. Unique clinically relevant swine models of arrest exist for ventricular fibrillation, asphyxia, and hemorrhagic shock; however, a similar swine model does not exist for chemical-induced cardiac arrest.[11] The most recent American Heart Association advance cardiac life support guidelines recognize that cardiac arrest from poisoning differs substantially from that caused by other events.[12]

Hydroxocobalamin was approved in 2006 according to efficacy documented in both animal studies and human case series.[4,13] Hydroxocobalamin covalently binds cyanide to form the nontoxic metabolite cyanocobalamin (vitamin B_{12}), which is excreted in urine. Recent animal studies examined the effect of hydroxocobalamin on respiratory depression, a mild symptom of cyanide toxicity.[13] Our group has previously demonstrated the efficacy of hydroxocobalamin in cyanide-induced hypotension and compared its effects with that of the traditional antidote of sodium nitrite and sodium thiosulfate.[14] We have also shown that antidotes are not routinely used clinically in patients with cyanide-induced arrest or hypotension.[9] To our knowledge, hydroxocobalamin's effectiveness has not been evaluated in cyanide-induced cardiopulmonary arrest, where its benefit could be most valuable.

Goals of This Investigation

The purpose of our study was to compare survival and mean arterial pressure between 3 groups of swine treated with intravenous hydroxocobalamin, epinephrine, and saline solution control in a model of acute cyanide-induced cardiac arrest. Our primary hypothesis was that hydroxocobalamin would improve survival compared with saline solution in a cyanide-induced cardiac arrest swine model and be equal to epinephrine. Secondary parameters that were evaluated between groups included coronary perfusion pressure, blood cyanide and lactate levels, bicarbonate, troponin, and the continued need for more epinephrine infusions as vasopressor support.

MATERIALS AND METHODS

Study Design and Setting

We conducted a randomized comparative laboratory investigation. The study was approved by our Institutional Animal Care and Use Committee. All procedures involving animals complied with the regulations and guidelines of the Animal Welfare Act, the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and the American Association for Accreditation of Laboratory Animal Care. The housing of animals and the performance of the study took place in the Animal Care Facility at our institution.

Selection of Participants

Forty-five Yorkshire swine (38 to 42 kg) of both sexes were premedicated with intramuscular ketamine 10 mg/kg. General anesthesia was induced with isoflurane by nose cone and, after tracheal intubation, maintained through the study with inhaled isoflurane (1% to 3%) and oxygen FiO_2 of 0.4 to 0.45. The animals were mechanically ventilated with a volume-limited, time-cycled ventilator (Fabius GS anesthesia machine; Drager-Siemens, New York, NY). The tidal volume was initially 10 to 12 mL/kg and respiratory rate 12 breaths/min. The minute ventilation was adjusted to maintain an end tidal CO_2 value between 38 and 42 mm Hg, as measured by inline capnography. Lead II of the surface ECG was monitored continuously. Temperature was maintained at 37.5°C (99.5°F) to 39°C (102.2°F). Baseline biochemical markers were measured (arterial blood gas, hematocrit, methemoglobin, and electrolytes). Baseline was defined as 1 minute before initiation of cyanide infusion.

Interventions

Aortic pressure was measured continuously through the femoral artery (model SPR407; Millar Instruments, Houston, TX). An 8.5-French introducer (Arrow, Reading, PA) was placed in the carotid artery for laboratory sampling and another

was placed in the femoral vein for medication administration. The introducers were flushed with heparinized saline solution. A Millar catheter was placed in the right external jugular to measure central venous and right atrial pressures. The Millar catheter allowed high-frequency, continuous, uninterrupted hemodynamic measurements during closed chest compressions. Coronary perfusion pressures were calculated (aortic diastolic blood pressure–right atrial diastolic pressure).[15] Heparin (100 U/kg) was administered intravenously after catheters were inserted. The Fabius GS anesthesia data storage software was used for data acquisition of all hemodynamic variables at 1-minute intervals.

Baseline biochemical measurements included oxygen saturation, PCO_2, PO_2, and pH (ABL 800 Flex blood gas analyzer; Radiometer America, Westlake, OH), methemoglobin and hemoglobin (Radiometer, OSM3 Hemoximeter), electrolytes (Piccolo Chemistry Analyzer; Abaxis, Union City, CA), lactate, and whole blood cyanide levels (Diagnostic Center for Population and Animal Health, Michigan State University, Lansing, MI).[14]

All animals received a warmed, saline solution, 15 mL/kg intravenous bolus and were acclimated for 30 minutes before the experiment. Isoflurane was then reduced to 1.5% to allow spontaneous ventilation, and a constant potassium cyanide mixture (0.4%) was infused until cardiac arrest. In our previous experiments, we found this cyanide dose effective in causing severe hypotension and 100% lethality if untreated while allowing animals to recover with antidotal treatment.[14] After 2 minutes of the cyanide infusion, mechanical ventilation was halted and animals continued to spontaneously breathe isoflurane. Apnea was defined as more than 15 seconds without a spontaneous respiration.

The cyanide infusion was stopped when cardiac arrest developed (mean arterial pressure less than 30 mm Hg for 30 seconds), mechanical ventilation was resumed, and oxygen was increased to FiO_2 of 1.0. Animals received a 20 mL/kg intravenous bolus of warmed normal saline solution and were then randomized to receive intravenous hydroxocobalamin (150 mg/kg), epinephrine (0.02 mg/kg), or saline solution (control).[16] The randomization was performed before we started the experiment, using a random number generator Web site. The investigators were not blinded. This dose for hydroxocobalamin and epinephrine was based on recent large-animal studies.[13,14,16] All groups received their treatments in an equal volume of 200 mL of volume. We infused 10 mL of saline solution flush before and after treatment administration (20 mL in each animal). Closed chest compressions were performed with the Thumper compression device (Model 1007; Michigan Instruments, Grand Rapids, MI).[17] We defined return of spontaneous circulation as a systolic blood pressure greater than 60 mm Hg for 1 minute.[18] Vasopressor support with an intravenous epinephrine infusion (epinephrine 0.1 μg/kg per minute) was used in all arms after return of spontaneous circulation for a systolic blood pressure less than 90 mm Hg.

Table 1. Baseline data of instrumented animals immediately before cyanide infusion.*

Characteristics	Control (N=15)	Epinephrine (N=15)	Hydroxocobalamin (N=15)
Weight, kg	40 (2.6)	43 (2.1)	43 (2.4)
Pulse rate, beats/min	89 (9)	90 (17)	90 (9)
Systolic blood pressure, mm Hg	100 (11)	111 (13)	115 (14)
Mean arterial pressure, mm Hg	79 (10)	89 (12)	93 (12)
pH	7.42 (0.06)	7.40 (0.08)	7.46 (0.04)
Hemoglobin, g/dL	9 (0.6)	8.3 (1)	8.4 (1)
Lactate mmol/L	1.0 (0.36)	1.1 (0.63)	1.1 (0.55)

g/dL, Grams per deciliter; *Kg*, kilograms; *min*, minute; *mm*, millimeters; *mmol/L*, millimoles per liter; *SD*, standard deviation of the mean.
*Baseline was defined as 1 minute before initiation of cyanide infusion.

The infusion was titrated every 2 minutes by 0.1 μg/kg per minute to maintain a systolic blood pressure greater than 90 mm Hg. We monitored the animals for 60 minutes after cardiac arrest.

Chest compressions were interrupted every 5 minutes for assessments. If the systolic blood pressure was less than 60 mm Hg, then an epinephrine bolus (0.02 mg/kg) was administered, and mechanical chest compressions were continued for an additional 5 minutes. Death of an animal was defined as a mean arterial pressure less than 25 mm Hg for 10 minutes. The animals were killed with intravenous sodium pentobarbital according to the American Veterinary Medical Association Panel on Euthanasia guidelines.

Whole blood cyanide levels were measured with spectrophotometry (Diagnostic Center for Population and Animal Health).[19] This method generates hydrogen cyanide gas, converts it to a cyanogen chloride, and uses spectrophotometric determination of the barbituric acid complex.[19] This method does not measure cyanide bound as cyanmethemoglobin or cyanocobalamin. Whole blood hydroxocobalamin and cyanocobalamin levels were measured with liquid chromatography–tandem mass spectrometry.[20] Troponin I levels were measured with pig cardiac troponin I ELISA (enzyme-linked immunosorbent assay) (Life Diagnostics, Inc, West Chester, PA).

Methods of Measurement and Outcome Measures

The primary outcome measure was survival to 60 minutes after cyanide-induced cardiac arrest. Secondary outcome measures compared between groups included return of spontaneous circulation, need for and dose of vasopressor infusion, pulse rate, and pH, lactate, base excess, serum bicarbonate, troponin, creatine kinase-MB, and cyanide levels.

Vital signs and hemodynamic measurements were recorded at 1-minute intervals and analyzed at 5-minute intervals. Serum blood sampling was taken at baseline, 10 minutes after cyanide infusion start, at cardiac arrest, and at 10-minute intervals after arrest until 60 minutes.

Table 2. Cyanide dosing and interval data at apnea and cardiac arrest.*

Characteristics at Apnea	Control (N=15)	Epinephrine (N=15)	Hydroxocobalamin (N=15)
Time to apnea, min:sec	5:53 (2:45)	6:52 (2:05)	6:14 (2:41)
Cyanide dose to apnea, mg/kg	1.13 (0.56)	1.19 (0.54)	1.21 (0.59)
Characteristics at cardiac arrest			
Cyanide dose, mg/kg	4.91 (1.3)	4.32 (1)	4.29 (1.2)
Time to cardiac arrest, min:sec	24:54 (6:40)	21:48 (4:54)	21:39 (5:53)
Cyanide level, μg/mL	4.26 (1.21)	4.0 (1.04)	4.0 (1.4)
pH	7.1 (0.12)	7.16 (0.15)	7.19 (0.12)
Lactate, mmol/L	7.5 (2.4)	6.9 (1.31)	7.1 (1.5)

*Data are presented as mean (SD).

Primary Data Analysis

Fisher's exact test or χ^2 was used to compare survival at 60 minutes, return of spontaneous circulation at 5 and 10 minutes, and the use of epinephrine infusion. For group size analysis, we assumed no animals would survive in our control group at 60 minutes. We calculated that with a 2-tailed α of .05 and 15 animals in each group, we had a power of 0.8 to detect a survival difference of 0.5 at 60 minutes compared with controls. Thus, we included 45 animals in our experiment. Power calculations were performed on G*3 Power (Erdfelder, Faul, & Buchner; Dusseldorf, Germany).

Values for blood pH, lactate, bicarbonate, serum cyanide concentrations, plasma sodium and potassium concentrations, troponin, and creatine kinase-MB were compared between groups with repeated-measures ANOVA for time zero to 60 minutes. Animals that died before 60 minutes after hypotension were excluded from this analysis. Statistical significance was set at $P<.05$, and all P values represent 2-tailed calculations. Statistical analyses were performed with SAS software (version 9.2; SAS Institute, Inc., Cary, NC).

RESULTS
Characteristics of Study Subjects

At baseline, all 3 groups had similar vital signs, weights, and biochemical markers (Table 1). The time to apnea, cyanide dose at apnea, time to arrest, cyanide dose at arrest, mean cyanide levels, lactate levels, and pH at arrest were also similar in all groups (Table 2). At arrest, the most common rhythm was junctional bradycardia or sinus bradycardia that degraded into asystole. Ventricular fibrillation occurred in 1 animal in the hydroxocobalamin arm. It started at 8 minutes after cardiac arrest and the animal died. ST-segment elevation occurred in most cases.

Main Results

No animal (0/15; 95% confidence interval [CI] 0% to 25%) in the control group survived to the end of the experiment. In both the hydroxocobalamin and epinephrine groups, 73% (11/15; 95% CI 48% to 90%) of the animals survived. Both treatments improved survival compared with the control group ($P<.001$). At 4 minutes after arrest, coronary perfusion pressures were greater than 15 mm Hg in both treatment groups, 18.4 (SD 10.1) in the hydroxocobalamin group and

28.9 (SD 8.4) in the epinephrine group. The proportion of animals with return of spontaneous circulation at 5 minutes was 4 of 15 (27%; 95% CI 10% to 52%) in each group, and return of spontaneous circulation at 10 minutes was 11 of 15 (73%; 95% CI 48% to 90%) in each group. All animals in the epinephrine group (11/11; 100%; 95% CI 70% to 100%) and 2 animals in the hydroxocobalamin group (2/11; 18%; 95% CI 4% to 48%) required additional epinephrine infusions for hypotension after return of spontaneous circulation.

Lactate, pH, bicarbonate, and cyanide levels improved from arrest to 60 minutes in the hydroxocobalamin group compared with epinephrine (Figure 1A to D). At 60 minutes, mean serum lactate, bicarbonate, cyanide, and pH levels were all significantly improved in the hydroxocobalamin group (Table 3). Cyanide levels were undetectable beginning 10 minutes after cardiac arrest until the end of the experiment in the hydroxocobalamin group.

Blood troponin and creatine kinase-MB levels were similar in both treatment groups. Levels increased from baseline to arrest and decreased after treatment administration until experiment end (Figure 2A, B).

Hydroxocobalamin blood levels peaked at 10 minutes after arrest (488 μg/mL; SD 147 μg/mL). Cyanocobalamin levels also peaked at 10 minutes after arrest (172 μg/mL; SD 43 μg/mL).

LIMITATIONS

The primary limitation of our study is that an animal model does not precisely reproduce human toxicity. We chose a swine model because it has been used in previous investigations of cyanide toxicity and because the swine cardiovascular system is analogous to that of humans.[11,21] Another limitation is the use of intravenous cyanide as a substitute for the more common exposure of inhalation. Both have rapid onset, but the intravenous route provided a more controlled way of inducing toxicity without the large loss of life that might be associated with the relatively uncontrolled absorption through an inhalational model of cyanide poisoning. This limitation was minimized by establishing a clinical endpoint, cardiopulmonary arrest defined by a mean arterial blood pressure of less than 30 mm Hg, and by measuring cyanide levels to ensure that toxic concentrations similar to those observed in humans were achieved. In addition, the inhalational route could put the research staff at a greater risk than the intravenous route because of undetected leaks in the ventilation system.[13,22]
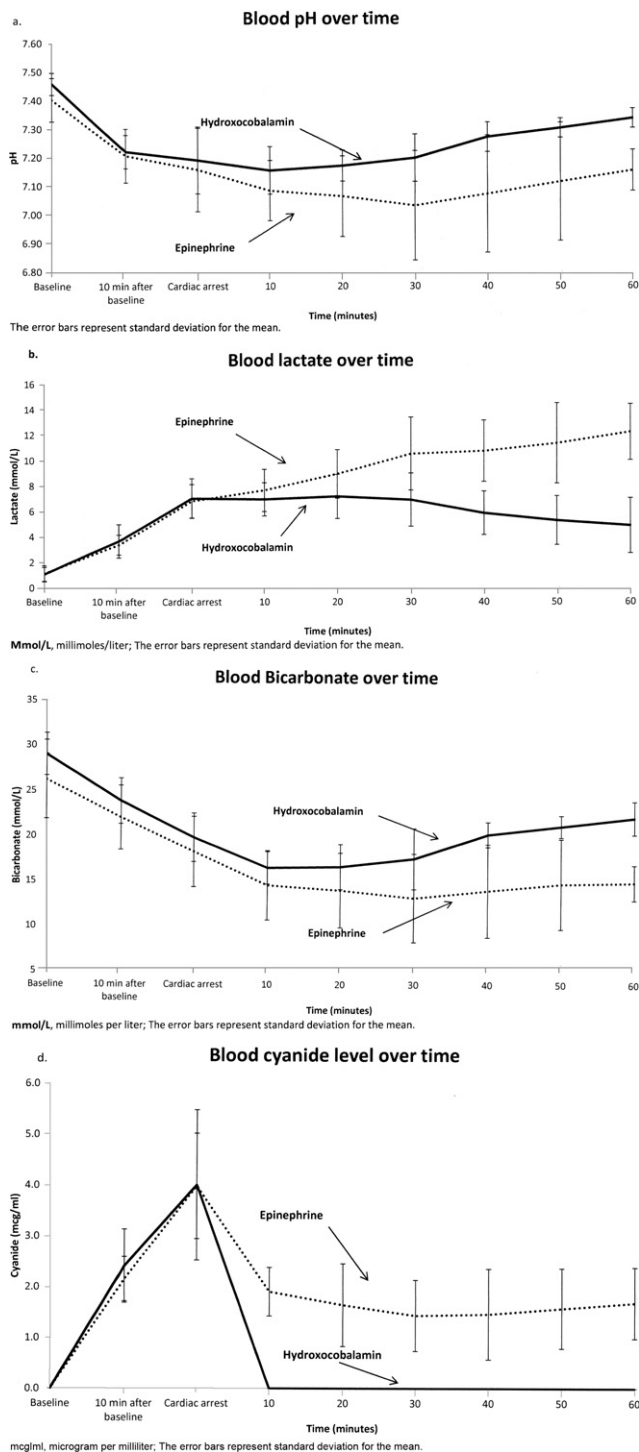
Figure 1. Blood pH, lactate, bicarbonate, and cyanide levels over time. N = 11 animals in each treatment group.

Table 3. Laboratory values at the end of the experiment (60 minutes after treatment).

	Epinephrine (N=11)	Hydroxocobalamin (N=11)
Hemodynamic measurements		
Pulse rate, beats/min	163 (18)	143 (20)
Systolic blood pressure, mm Hg	98 (22)	110 (10)
Mean arterial blood pressure, mm Hg	78 (14)	89 (8)
Laboratory values		
Cyanide level, μg/mL	1.8 (0.48)	0
pH	7.15 (0.07)	7.34 (0.03)
Lactate, mmol/L	12.3 (2.2)	4.9 (2.2)
Bicarbonate, mmol/L	15 (2)	22 (1.8)
Base excess, mEq/L	−11.2 (2.6)	−2.5 (2.3)

Data are presented as mean (SD).
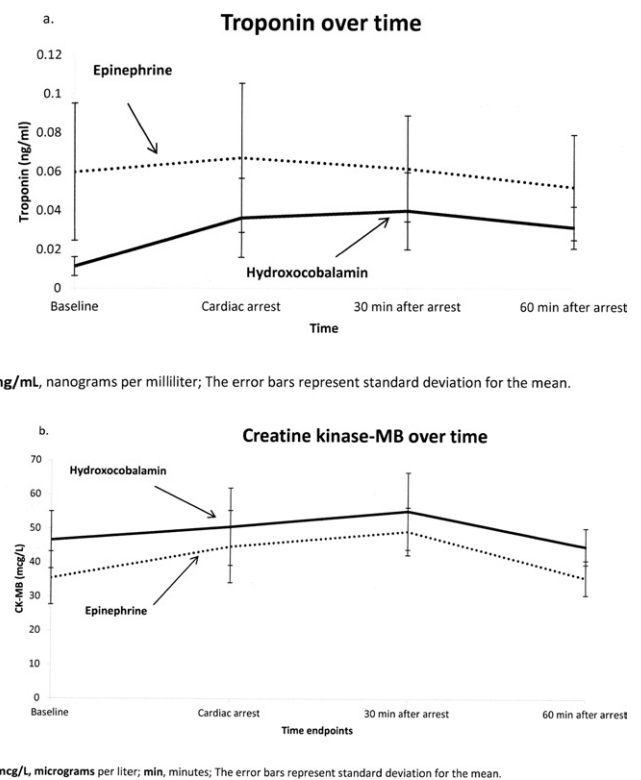
Figure 2. Troponin and creatine kinase-MB fraction over time.

Observing the animals for a longer period could have resulted in other differences between groups for both biochemical markers and hemodynamic measurements. However, by 60 minutes the differences in groups were clear. Neurologic effects were not measured in this preliminary study. Oxygen therapy has been used as a sole treatment for cyanide toxicity; however, both groups received oxygen therapy similar to that used in clinical practice.[23]

We used inhalational anesthetic, which can cause hypotension; however, we used a low dose of isoflurane that was similar in both groups. We did not measure mixed venous oxygenation or cardiac output after cardia arrest but have reported the measurements after hydroxocobalamin in a model of cyanide-induced hypotension.[14] We did not blind the investigators; however, we used randomization and objective outcome measurements. Small differences in characteristics between groups at baseline, apnea, and

cardiac arrest were detected (Tables 1, 2, and 3). Although the differences were small, they may have influenced the outcomes. Finally, we did not study a combination of hydroxocobalamin and epinephrine after return of spontaneous circulation, which would likely be used together in cardiac arrest; however, our goal was to determine the specific role of hydroxocobalamin in improving cyanide-induced cardiac arrest.

DISCUSSION

Cyanide is a ubiquitous and lethal chemical that quickly induces cardiac arrest in most exposed patients. Our study showed that hydroxocobalamin and epinephrine are equally effective in improving survival in our model of cyanide-induced cardiac arrest. The hydroxocobalamin group showed improved acidemia and lactic acidosis, reduced cyanide levels, and improved blood pressure compared with the epinephrine group.

Although the implication of a reduction in cyanide levels is unclear in this toxic model, reducing cyanide levels may reduce the acidemia and lactate acidosis after resuscitation, as was evidenced in our study. In addition, cyanide is a neurotoxin and its duration in the circulation may correlate with the severity of its effects.[24] Reduction of circulating cyanide could mitigate neurologic effects, prevent recurrence of cardiotoxic effects, and lessen the inhibition of cellular respiration.

After cardiac arrest, lactate levels improved with hydroxocobalamin and worsened with epinephrine. This difference could have resulted from the removal of cyanide's inhibition of oxidative phosphorylation. The increased lactate level could also have been derived from epinephrine's direct vascular effects, including β-agonist effects of cumulative dosing, impairment of microcirculation, and altered organ clearance of blood lactate.[25,26]

Hydroxocobalamin has been reported to cause a significant immediate vasopressor effect in humans and animal studies, occasionally inducing high blood pressure after infusion, which we detected in our previous study.[14] Most of the animals in our hydroxocobalamin group also maintained a higher blood pressure without supplemental vasopressor infusion. A component of hydroxocobalamin's effectiveness is binding cyanide; however, this would not explain its immediate vasopressor effects. This immediate increase in blood pressure may be due to the nitric oxide scavenging effect of hydroxocobalamin.[27] Nitric oxide is released in cardiopulmonary arrest, and this scavenging effect is a possible cause for immediate blood pressure improvement.[28,29] The sustained pressor effect is likely a combination of nitric oxide scavenging, cyanide binding, and other effects that we do not completely understand.

We also explored the early cardiotoxic effects of cyanide in our study. Cyanide may cause myocardial toxicity by causing cellular asphyxia or inhibition of inotropy by unclear mechanisms or by direct toxicity to the myocardium (not through cellular respiration inhibition). Although all 3 of these causes are possible, no data have clearly demonstrated that cyanide is toxic to the myocardium. One case report

described 2 patients with myocardial infarction and elevated CK level; however, human or animal studies have not reported serial measurement of cardiac enzymes.[30] Even though our experiment was short and exploratory, we detected an increase in troponin and creatine kinase-MB levels early, which peaked at cardiac arrest and suggests that cyanide may be directly cardiotoxic. Additional research in this area is needed to elucidate cyanide's cardiotoxicity.

In one published care series, 50% of probable cyanide-toxic cases resulted in hypotension and cardiac arrest.[10] However, few experimental studies have evaluated cyanide-, drug-, or chemical-induced cardiac arrest. We created a model to evaluate this form of cardiopulmonary arrest. Unique, clinically relevant swine models for ventricular fibrillation, asphyxia, and hemorrhagic shock exist, but a similar swine model for drugs or chemical-induced cardiac arrest has not been established, to our knowledge. Our model consistently produced animals that were reproducibly critically ill, with a high lactate and low pH level. As expected, none of our saline solution control animals survived. The model is recoverable and, congruent with our previous study, allows comparison of drug treatments for cyanide toxicity.[14]

Our study was also unique because we were able to measure hydroxocobalamin levels. Cardiac arrest is a unique state for drug metabolism.[31,32] Measurement of these levels will allow us to better understand antidotes during cardiac arrest. The hydroxocobalamin levels peaked at 10 minutes, a time similar to that of our study of cyanide-induced hypotension; however, the mean levels in the current study were 50% of the levels detected in the animals with hypotension.[14] In addition, at 60 minutes after cardiopulmonary arrest, the levels were 60% of peak levels. In our previous study of hypotension, the levels were 50% of peak by 30 minutes. The lower hydroxocobalamin concentration may be due to reduced binding of cyanide to hydroxocobalamin as a result of the poor circulatory state. Cyanocobalamin levels peaked at 10 minutes after arrest, but this peak was also approximately 50% of the levels in our previous study of cyanide-induced hypotension.

In conclusion, hydroxocobalamin and epinephrine both improved survival compared with saline solution control in our swine model of cyanide-induced cardiac arrest. Hydroxocobalamin was also found to improve blood pressure and pH, decrease blood lactate and cyanide levels, and reduce the need for vasopressor therapy compared with epinephrine.

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